Received: 20 February 2021 | Accepted: 6 May 2021

DOI: 10.1111/ene.14912

european journal of neurology
the official journal of the european academy of neurology

REVIEW ARTICLE

Factors associated with COVID-19 in people with Parkinson's disease: a systematic review and meta-analysis

Diego Chambergo-Michilot[1,2,3] | Shamir Barros-Sevillano[4,5,6] | Oscar Rivera-Torrejón[7,8] | Gabriel A. De la Cruz-Ku[9] | Nilton Custodio[10]

[1]Facultad de Ciencias de la Salud, Escuela de Medicina Humana, Universidad Científica del Sur, Lima, Perú

[2]Department of Cardiology Research, Torres de Salud National Research Center, Lima, Peru

[3]Red Latinoamericana de Cardiología, Lima, Perú

[4]Tau-RELAPED Group, Trujillo, Perú

[5]Facultad de Ciencias de la Salud, Escuela de Medicina, Universidad César Vallejo, Trujillo, Perú

[6]Sociedad Científica de Estudiantes de Medicina de la Universidad César Vallejo, Trujillo, Perú

[7]Facultad de Medicina, Escuela de Medicina Humana, Universidad Nacional Mayor de San Marcos, Lima, Perú

[8]Sociedad Científica de San Fernando, Lima, Perú

[9]Department of Surgery, Mayo Clinic, Rochester, MN, USA

[10]Cognitive Neurology Center, Instituto Peruano de Neurociencias, Lima, Perú

Correspondence
Diego Chambergo-Michilot, Republica de Panama 348 Avenue, Lima, Peru.
Email: diegochambergomichilot@hotmail.com

Funding information
The authors declare that this study was self-funded.

Abstract

Background: There is debate as to whether there is an increased risk of COVID-19 infection in people with Parkinson's disease (PD), possibly due to associated factors. This study aimed to systematically review the factors associated with COVID-19 in people with PD.

Methods: A search was carried out in PubMed, Scopus, and Web of Science up to November 2020 (updated until 1 April 2021). Observational studies that analyzed factors associated with COVID-19 in people with PD were selected and revised.

Results: The authors included six studies (four case-controlled studies and two cross-sectional studies) in the qualitative and quantitative syntheses. The authors found that the following factors were associated with COVID-19 in people with PD: obesity (OR: 1.79, 95% CI: 1.07–2.99, I^2: 0%), any pulmonary disease (OR: 1.92, 95% CI: 1.17–3.15, I^2: 0%), COVID-19 contact (OR: 41.77, 95% CI: 4.77 – 365.56, I^2: 0%), vitamin D supplementation (OR: 0.50, 95% CI: 0.30–0.83, I^2: 0%), hospitalization (OR: 11.78, 95% CI: 6.27–22.12, I^2: 0%), and death (OR: 11.23, 95% CI: 3.92–32.18, I^2: 0%). The authors did not find any significant association between COVID-19 and hypertension, diabetes, cardiopathy, cancer, any cognitive problem, dementia, chronic obstructive pulmonary disease, renal or hepatic disease, smoking, and tremor.

Conclusions: Meta-analyses were limited by the number of events and some methodological limitations. Despite this, the authors assessed the available evidence, and the results may be useful for future health policies.

KEYWORDS
SARS-CoV-2, 2019 novel coronavirus, Parkinson's disease, primary parkinsonism, systematic reviews

INTRODUCTION

The 2019 coronavirus disease (COVID-19), the name given to the severe acute respiratory syndrome cause by SARS-CoV-2 virus, has affected the world since its first report at the end of 2019. To date there are more than 60 million confirmed cases worldwide, with 1.5 million deaths. Among infected people, approximately 51.9% are male, with an incubation period of approximately 5 days, and fever being the most frequent clinical manifestation (78.8%), followed by cough (53.9%), and malaise (37.9%) [1].

Among the factors associated with COVID-19, it has been reported that the most frequently associated comorbidity, both in severe and non-severe cases, is arterial hypertension, followed by diabetes mellitus, as well as immunosuppressive states in severe cases [2].

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder in the world behind Alzheimer's disease. The PD rate ranges from 113 to 873 cases per 100,000 people, and increases in line with aging, reaching a rate of 1132–3198 cases per 100,000 in people aged over 80 years [3]. The lowest prevalence has been reported in Asia, while the highest is in Europe. This may be due to the greater number of elderly people in Europe; however, considering only people aged over 80 years, South America has the highest prevalence of PD [3].

The impact of the COVID-19 pandemic has affected PD patients in different ways. The most expected way is the higher frequency of serious cases of COVID-19 due to the presence of a predominantly elderly population; moreover, the mandatory quarantine in some countries has also affected the population with PD in terms of worsening of symptoms.

There is a debate about whether there is an increased risk of COVID-19 infection in people with PD. Two decades ago, researchers reported the presence of antibodies against coronavirus in the cerebrospinal fluid of patients with PD, suggesting a certain relationship between both entities [4]. In addition, the coronavirus uses the spike protein to interact with angiotensin-converting enzyme 2 (ACE2), for which COVID-19 has a higher affinity [5]. The latter is important because ACE2 is found in high quantities in dopaminergic neurons, which are decreased in people with PD, and may be another cause for the worsening of pre-existing symptoms or a more severe COVID-19 infection [6]. Besides, some researchers have hypothesized that an alteration of the dopamine synthetic pathways could be related to the pathophysiology of COVID-19, placing people with PD at a possibly higher risk of contagion [7].

It is undeniable that PD is associated with an elderly population; however, the outcomes obtained do not depend only on age, but on other factors, such as the presence of diabetes and arterial hypertension, which were found in higher proportions in the population with PD compared to the population without PD [8]. To date, a review has not yet been conducted that systematically addresses the search for factors associated with COVID-19 in people with PD. Therefore, we aimed to systematically review the available evidence on this topic.

METHODS

This systematic review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the Cochrane Handbook for Systematic Reviews of Interventions. The protocol was registered in PROSPERO (CRD42020220852) and Figshare (http://bit.ly/3qpFSYM).

Search strategy

We searched for evidence up to 14 November 2020 in the following databases: PubMed, Scopus, and Web of Science. We updated the search up to 1 April 2021. The search strategies are available in Supplementary Material S1. We did not limit the search by publication date or language.

Inclusion criteria

We intended to include observational studies (cross-sectional studies, case-controlled studies, and cohorts) that analyzed factors associated with COVID-19 in people with PD. We excluded case reports, case series, reviews, letters to the editor, congress or conference abstracts, editorials, interviews, comments, and newspaper articles.

Study selection

One author (D.C.M.) downloaded all the references to an EndNote document in order to eliminate duplicates. Then, this author exported those references to the Rayyan QCRI webpage (https://rayyan.qcri.org/). Two reviewers (D.C.M., S.B.S.) independently screened titles and abstracts. They assessed the full-text version of selected articles to determine eligibility. This selection was performed using a prepiloted Microsoft Excel sheet. Any disagreement was resolved by consensus.

Data extraction

Two authors (D.C.M., S.B.S.) independently extracted the data of interest. For dichotomous outcomes, we extracted absolute and relative frequencies. The extraction was performed using a prepiloted Microsoft Excel sheet. Any disagreement was discussed and resolved by consensus. In the case of not reported data, we planned to contact with the articles' authors.

Risk of bias

Two authors (D.C.M., S.B.S.) assessed the methodological quality of included studies. We used the Newcastle-Ottawa Scale (NOS) or its adapted version for cross-sectional studies. The NOS assesses three domains: (1) selection of the study groups, (2) comparability of groups, and (3) exposure or outcome according to the study design. We gave one point for each item (two points for a comparability item) according to methodological adequacy. The NOS gives a maximum score of 9 points. We considered that a score of ≥7 meant low risk of bias, a score of 4–6 meant moderate risk of bias, and a score <4 meant high risk of bias. Any disagreement was discussed and resolved by consensus.

Data synthesis

Meta-analyses were performed using a random-effect model with the inverse variance method. We used the Paule–Mandel estimator and Hartung–Knapp–Sidik–Jonkman method for τ^2 and 95% confidence intervals (95% CIs) calculations, respectively [9,10].

For dichotomous outcomes we used odds ratios (ORs) with their 95% CIs. For continuous outcomes we calculated the mean difference by subtracting the mean controls from the mean of cases. Heterogeneity was described with the I^2 statistic [11]. An I^2 <30%, I^2 30–60%, and I^2 >60% defined low, moderate, and high heterogeneity, respectively. We pooled outcomes if occurring in at least two studies. If one or more outcomes could not be extracted from a study it was removed from the analysis. Meta-regressions could not be performed due to insufficient number of studies per meta-analysis. We conducted the analyses using the metabin and metacont functions of the meta library of R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

RESULTS

Selection and characteristics of studies

After duplicate removal we screened 322 records. Finally, we included six studies in the qualitative and quantitative syntheses (Supplementary Material S2). Four of six manuscripts were case-control studies [8,12-14] and the remainder were cross-sectional studies [6,15]. Three studies assessed Italian people [8,12,13], two studies assessed Spanish people [14,15] and one paper studied people from all continents, with about 80% of respondents from the United States [6]. Only three studies reported PD criteria, and it was based on the Movement Disorder Society Clinical Diagnostic Criteria for PD. The case definition, or exposed people in the case of cross-sectional studies, was PD patients with COVID-19. The control definition, or non-exposed people in the case of cross-sectional studies, was PD patients without COVID-19. The study of Brown, 2020 assessed adults with and without PD, and subdivided it by COVID-19 infection. Only two case-control studies reported matching factors, which were sex, age, and disease duration (Table 1).

Characteristics of studied subjects

Regarding the characteristics of assessed subjects, the sample size ranged from 21 to 5429 subjects. The proportions of males and females were balanced between the cases and controls. The mean/median age ranged from 65 (IQR: 40–89) to 75.9 (SD: 9.0) years in cases/exposed, and from 63.5 (SD: 12.6) to 75.05 (SD: 8.18) years in controls/non-exposed. Disease duration ranged from 6.3 (SD: 3.6) to 9.9 (SD: 6.4) years in cases/exposed, and from 6.1 (SD: 2.9) to 9.5 (SD: 6.8) years in controls/non-exposed (Table 2).

TABLE 1 Characteristics of included studies

Author	Year	Design	Country	Population	PD diagnosis criteria	COVID-19 diagnosis criteria	Case/exposed definition	Control/non-exposed definition	Matching factors
Del Prete	2020	Case-control study	Italy	PD patients	MDS-PD	Laboratory[a]	PD patients with COVID-19	PD patients without COVID-19	Age and disease duration
Fasano	2020	Case-control study	Italy	PD patients	MDS-PD	Confirmed: molecular test Probable: COVID-19-related symptoms	PD patient with confirmed/probable COVID-19	PD patients without COVID-19	NR
Brown	2020	Cross-sectional study	All continents[b]	PD and non-PD patients	NR	Self-report	Patients with COVID-19	Patients without COVID-19	DA
Santos-García	2020	Cross-sectional study	Spain	PD patients	NR	Laboratory[a]	PD patients with COVID-19	PD patients without COVID-19	DA
Cilia	2020	Case-control study	Italy	PD patients	NR	Laboratory[a]	PD patients with COVID-19	PD patients without COVID-19	Sex, age, and disease duration
Sainz-Amo	2020	Case-control study	Spain	PD patients	MDS-PD	Laboratory[a]	PD patients with COVID-20	PD patients without COVID-20	NR

Abbreviations: DA, does not apply; MDS-PD, Movement Disorder Society Clinical Diagnostic Criteria for PD; NR, not reported; PD, Parkinson disease.

[a]Authors did not specific a method.

[b]About 80% of responses were from the United States.

TABLE 2 Characteristics of population of included studies

Part 1

Group	Author	Year	Sample size (*n*)	Age (years)	Male (%)	Disease duration (years)
PD patients with COVID-19	Del Prete	2020	7	75.71 (8.90)[a]	57.14	9.29 (3.59)[a]
PD patients without COVID-19			14	75.05 (8.18)[a]	57.14	8.93 (3.05)[a]
PD patients with COVID-19	Fasano	2020	105	70.5 (10.1)[a]	52.4	9.9 (6.4)[a]
PD patients without COVID-19			1381	73.0 (9.5)[a]	57.2	9.5 (6.8)[a]
PD patients with COVID-19	Brown	2020	51	65 (40–89)[b]	47	≥3 years: 60%
PD patients without COVID-19			5378	68 (33–95)[b]	52	≥3 years: 70%
PD patients with COVID-19	Santos-García	2020	15	65.6 (9.4)[a]	47.1	6.8(4.9)[a]
PD patients without COVID-19			553	63.5 (12.6)[a]	46.7	8.5(5.5)[a]
PD patients with COVID-19	Cilia	2020	12	65.5 (8.9)[a]	41.7	6.3 (3.6)[a]
PD patients without COVID-19			36	66.3 (8.1)[a]	41.7	6.1 (2.9)[a]
PD patients with COVID-19	Sainz-Amo	2020	39	75.9 (9.0)[a]	59	8.9 (6.2)[a]
PD patients without COVID-19			172	73.9 (10.0)[a]	59	8.5 (5.6)[a]

Part 2

Group	Author	Smoking (%)	Obesity (%)	Hypertension (%)	Diabetes (%)	Cardiopathy (%)
PD patients with COVID-19	Del Prete	NR	NR	71.43	42.86	28.57
PD patients without COVID-19		NR	NR	0	7.14	14.29
PD patients with COVID-19	Fasano	5.7	18.1	41.9	7.6	NR
PD patients without COVID-19		4.6	10.9	38.7	8	NR
PD patients with COVID-19	Brown	5.9	NR	25	NR	20
PD patients without COVID-19		1.6	NR	31	NR	8.2
PD patients with COVID-19	Santos-García	6.7	NR	26.7	20	3
PD patients without COVID-19		8.3	NR	24.3	9.7	65
PD patients with COVID-19	Cilia	0	8.3	33.3	0	8.3
PD patients without COVID-19		8.3	5.5	44.4	5.5	13.9
PD patients with COVID-19	Sainz-Amo	NR	NR	49	21	15
PD patients without COVID-19		NR	NR	42	12	19

Part 3

		Neurologic symptoms	
Group	Author	Hoehn-Yahr stage (%)	Tremor (%)
PD patients with COVID-19	Del Prete	NR	NR
PD patients without COVID-19		NR	NR
PD patients with COVID-19	Fasano	2.2 (0.8)	NR
PD patients without COVID-19		2.2 (0.9)	NR
PD patients with COVID-19	Brown	NR	NR
PD patients without COVID-19		NR	NR

Pharmacotherapy						
Levodopa (%)	Dopamine agonist (%)	MAO-B inhibitors (%)	Amantadine (%)	ACH (%)	Duodopa infusion/ DBS (%)	Vitamin D use (%)
100	28.57	42.86	0	14.29	0	NR
92.86	71.43	42.86	28.57	0	0	NR
95.2	47.6	21.9	1	NR	NR	12.4
95.9	47	19.6	2	NR	NR	22.9
NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	0	NR	NR	NR
NR	NR	NR	82	NR	NR	NR
83.3	75	50	0	NR	8.3	NR
77.8	63.9	44.4	0	NR	2.8	NR
NR	23	44	5	NR	DBS: 10.3 Duodopa infusion: 7.7	15
NR	41	49	12	NR	DBS: 4.1 Duodopa infusion: 4.1	24

Cancer (%)	Renal or hepatic dysfunction (%)	Any pulmonary disease (%)	COPD (%)	COVID-19 contact (%)	Dyslipidemia (%)	Arrhythmia (%)
14.29	0	0	NR	42.86	NR	NR
7.14	14.29	0	NR	0	NR	NR
0.9	NR	5.7	5.7	NR	NR	NR
3.3	NR	1.7	1.7	NR	NR	NR
NR	NR	14	NR	NR	NR	NR
NR	NR	8.1	NR	NR	NR	NR
0	NR	14.3	NR	14.8	64.3	20
3.1	NR	9.4	NR		24.1	12.7
16.7	8.3	8.3	8.3	50	NR	NR
8.3	13.9	11.1	11.1	0	NR	NR
8	8	10	NR	NR	NR	NR
2	2	8	NR	NR	NR	NR

Continous rigidity (%)	Motor fluctuation (%)	Dyskinesia (%)	Falls (often) (%)
NR	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR

(Continues)

Part 3

		Neurologic symptoms	
Group	**Author**	**Hoehn-Yahr stage (%)**	**Tremor (%)**
PD patients with COVID-19	Santos-García	NR	73.3
PD patients without COVID-19		NR	55.1
PD patients with COVID-19	Cilia	1.8 (0.7)	50
PD patients without COVID-19		1.8 (0.6)	50
PD patients with COVID-19	Sainz-Amo	NR	NR
PD patients without COVID-19		NR	NR

Part 4

		Psychiatric symptoms				
Group	**Author**	**Bad mood/ depression (%)**	**Anxiety (%)**	**Pain (every day) (%)**	**Cognitive problems (%)**	**Dementia (%)**
PD patients with COVID-19	Del Prete	NR	NR	NR	NR	NR
PD patients without COVID-19		NR	NR	NR	NR	NR
PD patients with COVID-19	Fasano	NR	NR	NR	NR	NR
PD patients without COVID-19		NR	NR	NR	NR	NR
PD patients with COVID-19	Brown	NR	NR	NR	NR	NR
PD patients without COVID-19		NR	NR	NR	NR	NR
PD patients with COVID-19	Santos-García	57.1	60	26.7	38.5	6.7
PD patients without COVID-19		65.6	65.8	50.4	36.2	16.2
PD patients with COVID-19	Cilia	NR	NR	NR	0	0
PD patients without COVID-19		NR	NR	NR	8.3	8.3
PD patients with COVID-19	Sainz-Amo	NR	NR	NR	36	36
PD patients without COVID-19		NR	NR	NR	14	14

Abbreviations: ACH, anticholinergic; COPD, chronic obstructive pulmonary disease; DBS, deep brain stimulation; MAO-B, monoamine oxidase B; NR, not reported; PD, Parkinson's disease.

[a]Mean (standard deviation).

[b]Median (interquartile range).

Regarding comorbidities, the ranges of prevalence of obesity, hypertension, diabetes, cancer, and any pulmonary disease were 8.3%–18.1%, 25.0%–71.43%, 0%–42.86%, 0%–14.29%, and 0%–14.3% in cases/exposed, respectively, and 5.8%–10.9%, 0%–44.4%, 5.5%–12.0%, 2.0%–8.3%, and 0%–11.1% in controls/non-exposed, respectively. Regarding PD-related symptoms, prevalence of tremor ranged from 50.0% to 73.3% in cases/exposed, and from 50.0% to 55.1% in controls/non-exposed. Three studies reported worsening of symptoms in the whole group (cases and controls). Following the onset of the pandemic, the prevalence

Continous rigidity (%)	Motor fluctuation (%)	Dyskinesia (%)	Falls (often) (%)
33.4	35.7	53.3	0
41.4	61	55.9	17.8
NR	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR

		Worsening following the onset of the pandemic					
Hallucinations (%)	Behavioral disorders (%)	Motor symptoms (%)	Mood (%)	Anxiety (%)	Sleep disorders (%)	Hospitalization (%)	Death (%)
NR	NR	29.6	24.7	25	22.2	57.14	14.29
NR	NR					0	0
NR	NR	NR	NR	NR	NR	17.1	5.7
NR	NR	NR	NR	NR	NR	27.2	7.6
NR	NR	55	51	NR	59	9.8	NR
NR	NR	41	30	NR	32	NR	NR
0	15.4	40.7	NR	31.3	41.4	5	0
23.4	33.6		NR			NR	NR
NR	NR	NR	NR	NR	NR	NR	0
NR	NR	NR	NR	NR	NR	NR	0
NR	NR	NR	NR	NR	NR	NR	21
NR	NR	NR	NR	NR	NR	NR	NR

of worsening of motor symptoms ranged from 29.6% to 41.13% [6,8,15], prevalence of worsening of mood was 24.7% and 30.19% (two studies) [6,8] prevalence of worsening of anxiety was 25% and 31.3% (two studies) [8,15] and prevalence of worsening sleep disorders ranged from 22.2% to 41.4% [6,8,15] (Table 2).

Concerning the outcomes, hospitalization prevalence ranged from 17.1% to 57.14% in cases/exposed, and from 0% to 9.8% in controls/non-exposed. Death ranged from 0% to 21% in cases, and from 0% to 7.6% in controls/non-exposed (Table 2).

TABLE 3 Risk of bias assessment of included case-controlled studies

			Selection				Comparability	Exposure			
Author	Year	Design	Case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability based on design or analysis	Ascertainment of exposure	Same method of ascertainment	Non-response rate	Quality score
Del Prete	2020	Case-control study	1	1	1	1	0	1	1	0	6
Fasano	2020	Case-control study	1	1	1	1	1	1	1	0	7
Cilia	2020	Case-control study	1	1	1	1	0	1	1	0	6
Sainz-Amo	2020	Case-control study	1	1	1	1	2	1	1	0	8

Meta-analyses of associated factors

In our crude meta-analyses, we found that the following factors were associated with COVID-19 in people with PD: obesity (OR: 1.79, 95% CI: 1.07–2.99, I^2: 0%), any pulmonary disease (OR: 1.92, 95% CI: 1.17–3.15, I^2: 0%), COVID-19 contact (OR: 41.77, 95% CI: 4.77–365.56, I^2: 0%), vitamin D supplementation (OR: 0.50, 95% CI: 0.30–0.83, I^2: 0%), hospitalization (OR: 11.78, 95% CI: 6.27–22.12, I^2: 0%), and death (OR: 11.23, 95% CI: 3.92–32.18, I^2: 0%). We did not find significant association between COVID-19 and the following factors: hypertension, diabetes, cardiopathy, cancer (Supplementary Material S3), any cognitive problem, dementia, chronic obstructive pulmonary disease, renal or hepatic disease, smoking, and tremor. Moreover, we did not find differences in Hoehn and Yahr scale results between cases and controls (Supplementary Material S4).

We pooled the prevalence of COVID-19 in PD patients (only cross-sectional studies) and this was 2% (95% CI: 0%–4%, I^2: 90%) (Supplementary Material S5).

Risk of bias

Regarding case-control studies, two studies presented problems in the comparability domain since they did not control their analysis for important factors [8,13]. None of these studies reported the non-response rate. Two of four studies presented a quality score lower than 7 points (Table 3).

Regarding cross-sectional studies, one study did not describe the non-response rate. The other study did not control its analysis for the most important factors. One of two studies presented a quality score lower than 7 points (Supplementary Material S6).

DISCUSSION

Key messages

First, we found that prevalence of COVID-19 in PD was 2%. Second, obesity, any pulmonary disease, hospitalization, and death were associated with COVID-19 cases. Moreover, vitamin D supplementation was associated with lower cases of COVID-19. However, more prospective and experimental studies are needed to address the factors associated with COVID-19 in PD.

Comparison with other studies

We found that pooled prevalence of COVID-19 in people with PD was 2%. In contrast, the reported prevalence in dementia patients was 13% [16]. First, dementia is a syndrome, therefore it accounts for PD and more neurodegenerative diseases. Second, the quantitative synthesis of this result comes from two studies, so the real

estimate may be greater. The latter is hypothesized since COVID-19 occurs frequently in older adults and comorbid adults [1] as well as PD, therefore it may influence the prevalence of the disease in PD. More studies are needed to provide evidence as to the real estimate of COVID-19 in PD.

Through our meta-analyses, we reported that obesity was an associated factor with COVID-19 in PD. This finding is consistent with the literature. Previous reports have shown that prevalence of obesity in COVID-19 is up to 61.3% [17]. Furthermore, previous papers have reported a potential association between obesity and the infection [18]. Obese people may present increased inflammatory cytokines that can alter the immune defense. Reduction in Th-2 and regulator cells has been reported, as well as an expansion of memory T-cells in fat tissue, and pro-inflammatory changes in the amount of adipokine, leptin, and adiponectin [18], which increase the probability of infection.

We reported that the presence of any other pulmonary disease in patients with PD was associated with COVID-19 cases. This is consistent with the literature in the general population [1]. Several pulmonary diseases injure the lung physiology, increase the risk of infection, and contribute to disease severity, such as asthma, which alters the immune system since innate and specific immunity are retarded, exacerbating the disease and increasing the risk of viral infection [19]. However, these results may not be sufficiently precise in terms of reality due to the small population in some included studies, such as that shown with chronic obstructive pulmonary disease, which was only reported in two studies [12,13], in one of which there was a population of 48 people and with a greater number of events in the group of people without COVID-19, a result contrary to that reported in other studies conducted in the general population without PD [13,20].

We found that vitamin D supplementation was associated with lower cases of COVID-19 in PD. Similarly, a previous meta-analysis in adults with unknown PD prevalence showed that vitamin D deficiency in COVID-19 was higher than in non-COVID-19 patients [21]. Vitamin D modulates the adaptive response since it regulates excessive cytokine production [22], β-defensins, and cathelicidins [23], which have an important role in inactivating viruses [24]. Nevertheless, this crude pooled result comes from non-randomized studies, and a self-report variable; moreover, patients did not declare frequency, and dose and administration mode of vitamin D, so the pharmacological properties must have been heterogeneous. Our result only suggests a probable benefit that must be confirmed by future randomized studies.

We found that a higher hospitalization rate was associated with the presence of COVID-19 in PD. Indeed, PD patients present a double risk of being admitted to hospital due to complications [25]. Likewise, in older adults, who are at higher risk of severe COVID-19, PD patients are at increased risk of comorbidities compared with non-PD patients [26]. Consequently, PD may predispose individuals to the risk of severe COVID-19, which leads to hospitalization. Furthermore, we found that mortality was associated with higher cases of COVID-19 in PD. This may be explained by the higher rate of intrahospital complications in PD patients, such as delirium, drug adverse effects, syncope, aspiration pneumonia, falls, and fractures [27]. Muscular weakness can early appear in PD [28], and it could contribute to respiratory failure, which leads to death.

On the one hand, after the pandemic onset, the prevalence of worsening of motor symptoms ranged from 29.6% to 41.13% [6,8,15]. Due to the pandemic and political measures, some treatments have been discontinued, such as aerobic exercise, which may explain the worsening of motor symptoms. On the other hand, non-motor symptoms have worsened too, such as emotional status (24.7%–30.19%), anxiety (25%–31.3%), and sleep disorders (22.2%–41.4%) [6,8,15]. Despite the fact that social isolation is a measure for preventing SARS-CoV-2 infection, it may be a potential factor of worsening of PD symptoms [29]. In fact, living during the pandemic is an external psychological stressor, mainly for the elderly. This has been explored in other studies in the first months since the onset of the pandemic, which reported that one of the main concerns perceived by people with PD was the possibility of becoming infected with COVID-19, in addition to the need for an evaluation by their neurologist for a dose readjustment or by their physical therapist [30,31].

Telemedicine has assumed an important role during the pandemic by permitting remote management [29], however, it is not sufficient for PD patients since they require physical follow-up on account of their motor symptoms. More efforts are needed to control worsening symptoms, especially in PD patients living in remote areas.

Relevance for public health

To our knowledge, this is the first systematic review that assessed factors associated with COVID-19 in PD population. COVID-19 is a disease that increases mortality in PD. The latter involves mainly older adults, who are at higher risk of COVID-19. Social isolating is a well-known measure for preventing infectious diseases; however, there are counterproductive effects, especially in older adults. We have reviewed that stress levels and worsening symptoms may be caused by this isolation and increase the risk of complications by reducing patients' quality of life. Novel health policies for PD are needed to prevent complications.

Limitations

Our review has several limitations. There were chronic diseases, like hypertension, diabetes, and cardiopathies, which did not show a significant association with COVID-19 in PD. Meta-analyses were limited by the number of events; moreover, in some studies, the case–control matching was not reported, so there were methodological limitations. In contrast, the literature indicates that these comorbidities are associated with severe COVID-19 in not or unknown PD patients [2]. Another limitation is that studies did not separate

the COVID-19 outcome by severity. Performing a subanalysis by severe COVID-19 might have better explained the plausibility of the association in some cases, such as obese patients. Moreover, meta-analyses were not adjusted for confounders. Despite these limitations, we broadly assessed the available evidence, and our results may be useful for future health policies.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Diego Chambergo-Michilot: Conceptualization (lead); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Shamir Barros-Sevillano:** Methodology (equal); Writing-original draft (equal); Writing-review & editing (equal). **Oscar Rivera-Torrejón:** Writing-original draft (equal); Writing-review & editing (equal). **Gabriel A. De la Cruz-Ku:** Writing-original draft (equal); Writing-review & editing (equal). **Nilton Custodio:** Writing-original draft (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Diego Chambergo-Michilot https://orcid.org/0000-0002-3904-7514

REFERENCES

1. Li J, Huang DQ, Zou B, et al. Epidemiology of COVID-19: a systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. *J Med Virol*. 2021;93(3):1449-1458.
2. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect*. 2020;81(2):e16-25.
3. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. 2014;29(13):1583-1590.
4. Fazzini E, Fleming J, Fahn S. Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. *Mov Disord Off J Mov Disord Soc*. 1992;7(2):153-158.
5. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 2020;367(6483):1260-1263.
6. Brown EG, Chahine LM, Goldman SM, et al. The effect of the COVID-19 pandemic on people with Parkinson's disease. *J Park Dis*. 2020;10(4):1365-1377.
7. Orrù G, Conversano C, Malloggi E, Francesconi F, Ciacchini R, Gemignani A. Neurological complications of COVID-19 and possible neuroinvasion pathways: a systematic review. *Int J Environ Res Public Health*. 2020;17(18):6688.
8. Del Prete E, Francesconi A, Palermo G, et al. Prevalence and impact of COVID-19 in Parkinson's disease: evidence from a multi-center survey in Tuscany region. *J Neurol*. 2021;268:1179-1187.
9. Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study 2 variance and its uncertainty in meta-analysis. *Res Synth Methods*. 2016;7(1):55-79.3.
10. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14:25.
11. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
12. Fasano A, Cereda E, Barichella M, et al. COVID-19 in Parkinson's disease patients living in Lombardy, Italy. *Mov Disord*. 2020;35(7):1089-1093.
13. Cilia R, Bonvegna S, Straccia G, et al. Effects of COVID-19 on Parkinson's disease clinical features: a community-based case-control study. *Mov Disord*. 2020;35(8):1287-1292.
14. Sainz-Amo R, Baena-Álvarez B, Pareés I, et al. COVID-19 in Parkinson's disease: what holds the key? *J Neurol*. 2020;1-5.
15. Santos García D, Oreiro M, Pérez P, et al. Impact of COVID-19 pandemic on Parkinson´s disease: a cross-sectional survey of 568 Spanish patients. *Mov Disord*. 2020;35(10):1712-1716.
16. Bianchetti A, Rozzini R, Guerini F, et al. Clinical presentation of COVID19 in dementia patients. *J Nutr Health Aging*. 2020;1-3.
17. Huang Y, Lu Y, Huang Y-M, et al. Obesity in patients with COVID-19: a systematic review and meta-analysis. *Metabolism*. 2020;113:154378.
18. Milner JJ, Beck MA. The impact of obesity on the immune response to infection. *Proc Nutr Soc*. 2012;71(2):298-306.
19. Wark PAB, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med*. 2005;201(6):937-947.
20. Gerayeli FV, Milne S, Cheung C, et al. COPD and the risk of poor outcomes in COVID-19: a systematic review and meta-analysis. *EClinicalMedicine*. 2021;33:100789.
21. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. *Crit Rev Food Sci Nutr*. 2020;1-9.
22. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients*. 2015;7(6):4240-4270.
23. Wang T-T, Nestel FP, Bourdeau V, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J Immunol Baltim Md 1950*. 2004;173(5):2909-2912.
24. Gropp R, Frye M, Wagner TO, Bargon J. Epithelial defensins impair adenoviral infection: implication for adenovirus-mediated gene therapy. *Hum Gene Ther*. 1999;10(6):957-964.
25. Temlett JA, Thompson PD. Reasons for admission to hospital for Parkinson's disease. *Intern Med J*. 2006;36(8):524-526.
26. McLean G, Hindle JV, Guthrie B, Mercer SW. Co-morbidity and polypharmacy in Parkinson's disease: insights from a large Scottish primary care database. *BMC Neurol*. 2017;17(126):1–8.
27. Lubomski M, Rushworth RL, Tisch S. Hospitalisation and comorbidities in Parkinson's disease: a large Australian retrospective study. *J Neurol Neurosurg Psychiatry*. 2015;86(3):324-330.
28. Baille G, Perez T, Devos D, Deken V, Defebvre L, Moreau C. Early occurrence of inspiratory muscle weakness in Parkinson's disease. *PLoS One*. 2018;13(1):e0190400.
29. Fasano A, Antonini A, Katzenschlager R, et al. Management of advanced therapies in Parkinson's disease patients in times of humanitarian crisis: the COVID-19 experience. *Mov Disord Clin Pract*. 2020;7(4):361-372.
30. Hanff A-M, Pauly C, Pauly L, et al. Unmet needs of people with Parkinson's disease and their caregivers during COVID-19-related confinement: an explorative secondary data analysis. *Front Neurol*. 2020;11:615172.

31. Cavallieri F, Sireci F, Fioravanti V, et al. Parkinson's disease patients' needs during the COVID-19 pandemic in a red zone: a framework analysis of open-ended survey questions. *Eur J Neurol*. 2021;00:1-9.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Chambergo-Michilot D, Barros-Sevillano S, Rivera-Torrejón O, De la Cruz-Ku GA, Custodio N. Factors associated with COVID-19 in people with Parkinson's disease: a systematic review and meta-analysis. *Eur J Neurol*. 2021;00:1–11. https://doi.org/10.1111/ene.14912